REMARKS

No amendment has been made herein. As such, claims 18-20 and 33-38 are currently under consideration.

Status of Application/Amendment/Claims

Applicants thank the Office for considering the arguments/amendments filed on March 25, 2008, and withdrawing the rejection under 35 U.S.C. § 112.

Priority

Applicants thank the Office for acknowledging and according the pending claims the priority date of February 20, 2002, on which U.S. Provisional Application No. 60/358,580 was filed.

Claim rejections under 35 U.S.C. § 103(a)

Claims 18-20 and 33-38 remain rejected as allegedly being obvious over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Matulic-Adamic *et al.* (US 5,998,203), Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031).

At the outset, it is respectfully submitted that, whilst it is known that terminal cap moieties and many chemical modifications can improve the nuclease ***stability*** of a nucleic acid inhibitor, whether that stability is compatible with ***activity*** must be determined on a molecule-by-molecule basis because improved stability does not correlate with improved or sustained activity. This lack of correlation exists in the ribozyme and antisense contexts, but perhaps even more prominently in the siRNA context because stability and binding affinity to the target is ***not*** what determines activity. Contrary to the Office's contentions, the molecule-by-molecule determination cannot be made with routine experimentation because there are many more chemical modifications known to confer stability than those which the Office has cherry-picked from the art in view of the instant claims, and whether and/or how each might be incorporated without compromising activity are by no means certain in each case.

It is respectfully submitted that the Office fails to recognize that a successfully designed siRNA molecule is to have at least two therapeutically relevant properties: stability and activity.

A highly stable siRNA molecule without activity is of no use to those skilled in the art. The Office appears to focus, without regard to ***activity***, extensively on chemical modifications and terminal cap moieties that were known to confer improved ***stability***, alleging that active molecules can be sorted from the inactive ones by routine experimentation. For example, the Office repeatedly alleges that Matulic-Adamic (in the context of the ribozyme art) teaches modifications and terminal cap moieties, which "protect nucleic acids from exonuclease degradation ... improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules," implying that the improved stability alone would induce a skilled person to test various modifications. *See, e.g.,* Final Office Action, at page 7; page 11; and elsewhere. The Office took no notice that the number of possible modified molecules having one or more terminal cap moieties is enormous and a skilled person ***would have no way of predicting*** whether a particular modified and capped molecule would be active ***prior to actually testing*** that molecule for RNAi activity. The Office sought support from Crooke for this "routine experimentation" argument, which is, as explained below, essentially an "obviousness to try" argument, stating that "Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration ... [which] is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity." *See* Final Office Action, at page 8. The Office further relied on Elbashir as evidence that "testing of such known chemical modifications is routine in the art." *See* Final Office Action, at page 10.

Applicants respectfully but strongly disagree. The Office fails to consider the fact that Crooke tested gapmer ***patterns*** for antisense activities, never venturing beyond a single type of 2'-sugar modification, a 2'-O-methyl, on that gapmer, even though the inventors/applicants of Crooke clearly had knowledge of ***a vast number of other stabilizing modification types*** in the art. *See* Crooke, at columns 4-7, 12-13, and Examples 10-16. In fact, Crooke emphasizes that, in the antisense context, it is important not only to the pick the right modification(s), but also to position these modifications at the right place(s) on the molecule because otherwise the molecule would be inactive. *See* Crooke, at column 48 ("although the 2'-modified oligonucleotides hybridized with greater affinity to RNA than did unmodified 2'-deoxy oligos they were completely ineffective in inhibiting Ha-ras gene expression."); at column 49 ("Fully modified 2'-methoxy oligonucleotides did not support nucleolytic cleavage of target mRNA and therefore did

not lead to a reduction in steady state levels of Ha-ras mRNA even at the highest concentration tested."). Therefore, even in the antisense context, the selection of an active and modified molecule requires the taking into account of at least two variables: the type(s) of modifications and the placement of the modifications on the molecules. Given the exceedingly numerous possibilities in each of the variables, finding active modified antisense molecules can hardly be said to be a routine undertaking, which potentially explains why Crooke had kept the modification variable fixed while testing only the pattern variable. Similarly, in Elbashir, only two out of a pool of hundreds (if not more) of known stabilizing chemical modifications were tested on a short interfering duplex. In that case, one, a 2'-deoxy, was found to sustain activity only if limitedly applied to the 3'-terminal residues, whereas the other, a 2'-O-methyl, was found to abrogate RNAi activity.

The Parrish reference indicates the same lack of correlation between stability and activity. For example, it was reported that one type of previously known modification, the alpha thiophosphate modification, causes chemical instability. *See* Parrish, at page 1081, right column ("modification of more than two residues greatly destabilized the RNAs in vitro and we were not able to assay interference activities."). A second type of known modification, the 2'-deoxy modification, cannot be applied to cytidines without substantially reducing RNAi. *See* Parrish, at page 1081, Figure 5B and right column ("Modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). A third and a fourth known types of modification, namely 2'-fluoro and 2'-amino, were reported to be compatible in the former instance if applied only to one strand of the duplex and to uridine but not cytidine amongst the pyrimidines, and was altogether incompatible in the latter instance. *See id.* at Figure 5B and right column ("Modification of uracil with 2'-fluorouracil was compatible with RNAi activity, while modification with 2'-aminouracil or 2'-aminocytidine produced a decrease in activity comparable to that seen with the deoxynucleotides modification."). Parrish also reported that RNA/DNA hybrids (*i.e.,* wherein all nucleotides of one strand of the duplex are modified with 2'-deoxy) do not mediate RNAi. *See id.* ("Such [RNA/DNA] hybrids were prepared synthetically and enzymatically and found to lack interference activity."). Accordingly, even in a long, 742-nt duplex, modifications known to enhance stability in other classes of nucleic acid inhibitors sometimes reduce stability and often kill activity.

In the haste to conclude routine experimentation or "obviousness to try," the Office has incorrectly applied the legal standard for obviousness. The U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007) touched upon the standard by which an "obviousness to try" or "routine experimentation" finding can serve as a basis for obviousness. Specifically, as later interpreted by the Court of Appeals at the Federal Circuit, an obviousness finding on that basis requires that the problem have "a finite number of identified, predictable solutions." *KSR,* 127, S. Ct. 1742; *see also, Abbott Laboratories v. Sandoz,* 2007-1300, *10 (Fed. Cir. October 21, 2008). As such, it is important to note the "clear difference between new biological compositions whose performance and effectiveness in combination ***cannot be confidently predicted [from the known elements in the art] but must be made and evaluated***, and new mechanical combination of known elements each of which predictably performs its known function in the combination." *Abbott,* at *10. (*emphasis added*). Here, the chemical modifications and terminal cap moieties were known in the art to enhance nuclease stability, but their effects on RNAi activity were not known and could not be confidently predicted. Indeed, as explained above, the cited references themselves indicated an utter lack of correlation between stability and activity in siRNA molecules when it comes to chemical modifications. Nor is this a case where there is a finite number of identified and predictable modification patterns from which active molecules can be routinely selected because there was a vast number of known modifications for nucleic acids at the time the present invention was made, and an even more vast number of possible arrangement of these modifications on a 18- to 27-mer duplex.

It is therefore submitted that those skilled in the art, knowing that stability-enhancing modifications ***cannot be predictably applied*** to a short siRNA molecule, would not have predicted that the terminal cap moieties, such as those found at the ends of a ribozyme molecule in Matulic-Adamic, can be applied without damaging RNAi activity. Enhanced stability alone simply does not serve as a motivation to modify an siRNA molecule, as there is nothing in the prior art to suggest whether and how modifications previously applied to other classes of nucleic acid molecules should be applied to a given siRNA molecule.

But even assuming, *arguendo,* that those skilled in the art could be motivated by the enhanced stability conferred by the terminal cap moieties in a ribozyme, they would have placed those moieties at all four ends of the siRNA molecule rather than selectively at the two ends of the sense strand and only optionally at the 3'-terminal end of the antisense strand, as is presently

claimed. There is nothing in the cited prior art to specifically indicate or suggest that this might be the pattern that preserves RNAi activity.

Accordingly, Applicants respectfully request the withdrawal of the outstanding obviousness rejection.

Double Patenting

Claims 18-20 and 33-38 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 15-18, 32, 36-40, 42-44 and 46-51 of copending Application No. 10/667,271. *See* Final Office Action, at page 16. Applicants respectfully note that the '271 Application has been abandoned as of July 21, 2008, according to the PAIR system, and therefore is no longer a co-pending application. As such, Applicants respectfully request withdrawal of the instant provisional non-statutory obviousness-type double patenting rejection.

Claims 18-20 and 33-38 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being allegedly unpatentable over claims 1-9, 13-20, and 23-39 of co-pending Application No. 10/664,668. *See* Final Office Action, at page 17. Applicants respectfully note that the '668 Application has been abandoned as of July 3, 2008, according to the PAIR system, and therefore is no longer a co-pending application. As such, Applicants respectfully request withdrawal of the instant provisional double patenting rejection.

Claims 18-20 and 33-38 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 3, 13-20, 31, 36-38 and 40-45 of co-pending Application No. 10/576,690. *See* Final Office Action, at page 18. Without acquiescing to the Office's contentions, Applicants have filed a Petition for Express Abandonment under 37 C.F.R. 1.138 in the '690 Application on December 23, 2008. As such, the '690 Application is no longer a co-pending application and Applicants respectfully request withdrawal of the instant provisional double patenting rejection.

Claims 18-20 and 33-38 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-10 and 13 of copending Application No. 11/684,465. Without acquiescing to the Office's contentions, Applicants have filed a Petition for Express Abandonment under 37 C.F.R. 1.138 in the '465 Application on December 17, 2008. As such, the '465 Application is no longer a co-pending

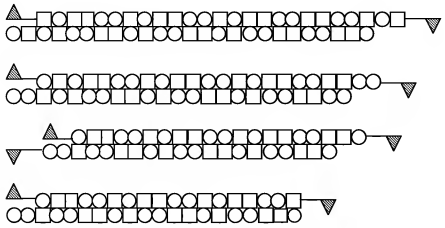
application and Applicants respectfully request withdrawal of the instant provisional double patenting rejection on that basis.

Claims 18-20 and 33-38 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being allegedly unpatentable over copending Application No. 11/369,108. Without acquiescing to the Office's contentions, Applicants have filed a Petition for Express Abandonment under 37 C.F.R. 1.138 in the '108 Application on December 17, 2008. As such, the '108 Application is no longer a co-pending application and Applicants respectfully request withdrawal of the instant provisional double patenting rejection.

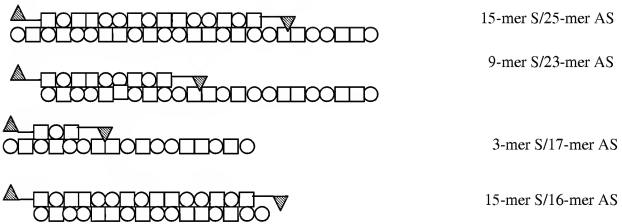
Claims 18-20 and 33-38 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being allegedly unpatentable over claims 1-9, 13-20, 23-29 and 31-35 of copending Application No. 10/567,888. Without acquiescing to the Office's contentions, Applicants have filed a Petition for Express Abandonment under 37 C.F.R. 1.138 in the '888 Application on December 16, 2008. As such, the '888 Application is no longer a co-pending application, and Applicants respectfully request withdrawal of the instant provisional double patenting rejection.

Claims 18-20 and 33-38 have been provisional rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 33-50 of co-pending Application No. 10/923,536. *See* Final Office Action, at page 22. Applicants respectfully traverse and submit that the Office has misread the claims of the '536 Application. Properly read, the claimed double stranded molecules therein do not have structural characteristics that overlap with those of the instantly claimed molecules, and the latter would not be obvious in view of the claims of the former.

Specifically, the instant claims are drawn to a chemically modified double stranded nucleic acid molecule, where each strand is 18-27 nucleotides in length, and 18-23 nucleotides of each strand are complementary to each other. The instantly claimed molecules further comprises terminal cap moiety at both ends of the sense strand, and optionally at the 3'-end of the antisense strand, wherein the terminal cap moieties are specifically enumerated. Representative claimed molecules are depicted below:



Comparing these to the molecules of the co-pending '536 application, the representatives of which are depicted below with the terminal cap moieties (in accordance with claims 37 and 38 of the '536 application):



It is therefore clear that the claimed molecules of the '536 application are mostly highly structurally asymmetrical, with the antisense strands being substantively longer than the sense strand. In an extreme example where the antisense strand is at its shortest and the sense strand is at its longest, as depicted in the last molecule above (15-mer S/16-mer AS), the lengths of the strands are significantly lower than the 18- to 27-mers claimed herein. As such, the molecules of the '536 application are not obvious variants of the herein claimed much longer molecules. As such, Applicants respectfully traverse the provisional obviousness-type double patenting rejection of the instant claims and request its withdrawal.

Conclusion

For the reasons stated above, Applicants respectfully request withdrawal of the outstanding rejections and objections and early allowance of the pending claims. If the Examiner believes a telephone conference would advance prosecution, she is urged to contact the undersigned at the number below.

Respectfully submitted,

Date: December 26, 2008

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